

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES



APPLICANT

: Jackowski et al.

INVENTION

: **Glycoprotein and Apolipoprotein
Biopolymer Markers Indicative of
Alzheimer's Disease**

SERIAL NUMBER

: 09/993,344

FILING DATE

: November 23, 2001

EXAMINER

: Chernyshev, Olga N.

GROUP ART UNIT

: 1649

OUR FILE NO.

: 2132.096

Mail Stop Appeal Brief-Patent
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

APPLICANTS' BRIEF IN ACCORDANCE WITH 37 C.F.R. § 41.37

Applicants submit this Appeal Brief to the Board of Patent Appeals and Interferences on appeal from the decision of Examiner Olga N. Chernyshev of Group Art Unit 1649 dated September 20, 2006, finally rejecting claim 1.

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I. REAL PARTY IN INTEREST

The real party in interest is Nanogen, Inc., the assignee of record.

II. RELATED APPEALS AND INTERFERENCES

Similar appeals have also been filed by Appellants in the following applications, all applications were filed on November 23, 2001; US Application Serial Numbers 09/991,796 (attorney docket number 2132.109), 09/991,799 (attorney docket number 2132.086) and 09/994,909 (attorney docket number 2132.090), which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

III. STATUS OF CLAIMS

Claims 1 and 39-46 are pending in the application. Claims 1-38 were originally presented. Claims 2-38 were cancelled without prejudice and new claims 39-46 were added by the amendment of June 9, 2003. Claims 39-46 were withdrawn from consideration on the merits based upon a restriction requirement. The final rejection of claim 1 under both 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph is appealed. Claim 1 is shown in the attached Claims Appendix.

IV. STATUS OF AMENDMENTS

No amendments have been filed subsequent to the Final Rejection mailed on September 20, 2006.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter relates to a biopolymer marker, identified by the evaluation of a sample containing a plurality of biopolymers, which evidences a link to a specific disease state. See, specification at page 35, lines 14-18. Specifically, the biopolymer marker consists of amino acid residues 2-18 of SEQ ID NO:1 and evidences a link to Alzheimer's disease. Id. at page 46, lines 11-19 and Figures 1 and 2.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

- A. Whether Claim 1 is Unpatentable under 35 U.S.C. § 101 as Having No Specific and Substantial Credible Utility
 - 1. Whether the Examiner Made a *Prima Facie* Showing that the Invention Lacks a Specific and Substantial Utility
 - 2. Whether the Examiner Properly Held that Applicants' Asserted Utility Lacks Credibility
- B. Whether Claim 1 is Unpatentable under 35 U.S.C. § 112, First Paragraph as Being Based on a Nonenabling Disclosure
 - 1. Whether the Examiner Properly Evaluated the Application for Enablement.

VII. ARGUMENT

A. The Examiner Erred in Rejecting Claim 1 under 35 U.S.C. § 101

1. The Examiner Has Failed to Make a Prima Facie Showing that the Invention Lacks A Specific And Substantial Utility.

Claim 1, as shown in the attached Claims Appendix, stands finally rejected under 35 U.S.C. § 101. The Examiner maintains that the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility.

Applicants respectfully traverse the rejection on the grounds that the application discloses an invention having specific, substantial, well-established and credible utility by showing an invention that is useful to the public as disclosed in its current form, rather than at some future date after further research, as a peptide marker linked to Alzheimer's disease. Furthermore, Applicants have supported this utility with data specifically directed to patients having Alzheimer's disease.

The standard for satisfying the requirements for utility under 35 U.S.C. § 101 is not particularly high. In most cases, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy 35 U.S.C. § 101. *See In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 297 (CCPA 1974); MPEP § 2107.02(III)(A). In other words, the Office is correct to presume that a statement of utility made by an applicant is true.

Accordingly, the Examiner should presume that the claimed peptide (amino acid residues 2-18 of SEQ ID NO: 1) is useful as a marker for Alzheimer's disease based upon Applicants' showing in Figure 1 that the peptide is linked to Alzheimer's disease by its

differential expression in Alzheimer's disease patients as compared to age-matched control patients.

A "specific utility" refers to a utility that is well-defined, particular and specific to the subject matter claimed. Vague expressions such as "a compound has useful biological activity" or "biological properties" are meaningless. In re Fisher, 421 F.3d 1365, 1371, 76 USPQ2d 1225 (Fed. Cir. 2005); In re Kirk, 376 F.2d 936, 941, 153 USPQ 48 (CCPA 1967); MPEP § 2107.01. For example, a general statement indicating that a marker is useful for diagnostics, such as diagnosing a disease, would be insufficient, absent a disclosure of what disease and/or condition could be diagnosed. In contrast, a statement of diagnostic utility, such as diagnosing Alzheimer's disease, would be sufficient to identify a specific utility for the invention. Thus, Applicants' statement of utility regarding the use of the claimed peptide as a marker for Alzheimer's disease constitutes a specific utility since the claimed peptide is linked to the specific condition of Alzheimer's disease.

It is well known that pathological changes in an organism are reflected by changes observed in the serum protein pattern. For example, proteins that undergo a change in expression (from the normal) are often indicative of disease. A diagnosis may be predicted based upon the similarity of an unknown sample pattern to a known pattern of disease. Mass spectrometry is a tool used to establish serum protein patterns.

Generally proteins, as collected from a serum sample, are too large to be effectively resolved by mass spectrometry and thus, are often first subjected to separation by polyacrylamide gel electrophoresis. Upon electrophoresis, the proteins contained in the sample separate into bands in specific areas of the gel according to weight and charge.

The separated protein bands which are observed and deemed to be different between two comparable states (for example, disease state vs. normal state) are excised from the gel and subjected to further fragmentation by enzymes. The resulting peptides are then collected and purified by chromatography prior to identification by mass spectrometry. The peptides undergo step-wise degradation into sequence-defining fragments, i.e. the peptides are part of the original protein found in the serum sample. The mass spectral profiles generated are composed of parts of the original protein and can be used to identify this protein.

In order for a rejection under 35 U.S.C. § 101 to be appropriate, the Examiner must demonstrate that there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention. In re Cortright, 165 F.3d 1353, 1355, 49 USPQ2d 1464 (Fed. Cir. 1999).

It is respectfully submitted that the "link to Alzheimer's disease" asserted by Applicants was elucidated under real-world conditions according to the methodology set forth in the following steps:

I. isolating peptides from body fluid samples obtained from two groups of patients; a) one group known to suffer from Alzheimer's disease; and b) a group of age-matched controls (healthy in regard to Alzheimer's disease);

II. carrying out the protocols disclosed in the specification on pages 37-47; ---

III. comparing the expression pattern of protein bands from the two groups of patients as evidenced in gels, such as that shown in Figure 1;

IV. subjecting the noted expression pattern to the criteria as disclosed in the specification at page 11, lines 9-20;

V. selecting and excising bands that are differentially expressed between the two groups, and, submitting the peptides present within the excised bands for further fragmentation and purification followed by sequence identification by mass spectrometry.

The Applicants, using the above-described methodology in a real-world environment, thereby elucidated and identified amino acid residues 2-18 of SEQ ID NO: 1 as a fragment of apolipoprotein J precursor protein found in age-matched control patients but absent in Alzheimer's patients, thus establishing the instantly claimed link to Alzheimer's disease evidenced by the observed differential expression.

The characteristic mass spectral profile indicative of the claimed peptide is disclosed in Figure 2 of the specification. Mass spectral profiles are reproducible and are typically published to provide established expression patterns for reference purposes.

Thus, any skilled artisan, in a real-world context, and without significant further research, could utilize the mass spectral profile provided in the instant specification as a reference for comparing with mass spectral profiles of peptides obtained from an unknown sample to test the unknown sample for a link to Alzheimer's disease through comparison of expression patterns, thereby demonstrating that the specification discloses a specific and substantial utility for the claimed peptide. This mass spectral profile is a showing of factual evidence that the claimed peptide could be used as a marker for Alzheimer's disease. Thus, data has been submitted supporting the desired results of the claimed invention; i.e. a biopolymer marker for Alzheimer's disease.

Accordingly, Applicants respectfully submit that the Examiner has failed to adhere to the precedent set in Cortright by failing to establish that there is a complete

absence of data supporting the statements which sets forth the desired results of the claimed invention.

The Examiner notes that in the instant case, the specification discloses the finding of differential expression of protein 2-18 of SEQ ID NO: 1 in samples of patients with AD vs. normal patients and presents an assertion that this protein 2-18 of SEQ ID NO: 1 is useful as a marker of Alzheimer's disease. The Examiner asserts that it is obvious that a skilled practitioner would have to engage in significant further research to establish what amount of the instant claimed protein is diagnostic of Alzheimer's disease. However, with regard to providing a link to Alzheimer's disease as is instantly claimed, it is well settled that an applicant is not required to provide evidence of an asserted utility as a matter of statistical certainty. Nelson v. Bowler, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980); MPEP § 2107.02.

Thus, Applicants respectfully submit that providing an amount of the claimed marker that is diagnostic for Alzheimer's disease is not necessary to establish credibility of the asserted use for the claimed peptide as a marker for Alzheimer's disease. Accordingly, Applicants respectfully submit that the Examiner's requirement for such information is improper.

A "substantial utility" is a utility that defines a "real-world" use. MPEP § 2107.01(I). "Substantial utility" refers to a significant and presently-available benefit to the public. An application must show an invention that is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. "In other words, one skilled in the art can use a claimed discovery in a manner which

provides some immediate benefit to the public.” Fisher, 421 F.3d at 1368, *citing Nelson*, 626 F.2d at 856.

In the context of an evaluation of substantial utility, the phrase "immediate benefit to the public" must not be interpreted to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. Brenner v. Manson, 383 U.S. 519, 534-535, 148 USPQ 689 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial utility". MPEP § 2107.01(I).

Additionally, care must be given not to find a lack of specific and substantial utility based upon the setting in which the invention is to be used. This is particularly important in biotechnology; for example, during examination of inventions to be used in a research or a laboratory setting. As the Federal Circuit noted:

“An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact ‘useful’ in a patent sense. [The PTO] must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.” Fisher, 421 F.3d at 1372, *citing* MPEP § 2107.01(I).

Many research tools such as gas chromatographs, screening assays and nucleotide sequencing techniques have a clear, specific and unquestionable utility, e.g., they are useful in analyzing compounds). MPEP § 2107.01(I).

Furthermore, it has been established that usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention becomes useful is well before it is ready to be administered to humans. If Phase II testing

was required in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. See In re Brana, 51 F.3d 1560, 1568, 34 USPQ2d 1436 (Fed. Cir. 1995); MPEP § 2107.01(III).

The identification of the presence of the claimed peptide in age-matched control patients and the absence (of the claimed peptide) in Alzheimer's disease puts a researcher one step closer to understanding the pathogenesis of Alzheimer's disease and thus, also one step closer to improved diagnosis and treatment of Alzheimer's disease. The claimed peptide can be used immediately to screen patient populations for links to Alzheimer's disease or it can be used in further research to improve diagnosis and treatment of Alzheimer's disease. There is no question that improved diagnosis and treatment of Alzheimer's disease provides a tangible benefit to society; especially for the elderly population susceptible to the development of Alzheimer's disease. Since the claimed peptide (amino acid residues 2-18 of SEQ ID NO: 1) has a "real-world" use in its currently available form as a marker for Alzheimer's disease, the claimed peptide thus has a substantial utility.

Accordingly, there is a critical distinction between an invention that can be used in further experimentation and research, and an invention that requires further experimentation and research before it can be used. Applicants respectfully submit that the Examiner has erroneously found the claimed invention to be the latter rather than the former.

The Examiner cites Fisher in rejecting claim 1 and attempts to draw a parallel to the instant application by asserting that, just as in Fisher - where the Board reasoned that the use of the claimed expressed sequence tags ("ESTs") for the identification of polymorphisms is not a specific and substantial utility because "[w]ithout knowing any further information in regard to the gene represented by an EST, as here, detection of the presence or absence of a polymorphism provides the barest information in regard to genetic heritage," Fisher, 421 F.3d at 1368 - the detection of peptide 2-18 of SEQ ID NO: 1 in samples of age-matched control patients and the absence of the peptide in Alzheimer's patients provides no meaningful information as to the diagnosis determination.

Applicants respectfully submit that the facts in Fisher are inapposite to those concerning the present application. Fisher's invention related to five purified nucleic acid sequences – ESTs - obtained from the leaf tissue of maize plants. As described in Fisher, an EST is a short nucleotide sequence that represents a fragment of a cDNA clone. It is typically generated by isolating a cDNA clone and sequencing a small number of nucleotides located at one end of the two cDNA strands. When an EST is introduced into a sample containing a mixture of DNA, the EST may hybridize with a portion of the DNA. Such binding shows that the gene corresponding to the EST was being expressed at the time of mRNA extraction.

Fisher disclosed in his application that the claimed ESTs may have been used in a variety of ways, including, for example, measuring the level of mRNA in a tissue sample via microarray technology to provide information about gene expression, isolating promoters and identifying the presence or absence of a polymorphism. Fisher, 421 F.3d at

1368. However, Fisher made no disclosure regarding the precise structure or function of either the genes or the proteins encoded for by those genes to which the claimed ESTs correspond. Id.

The Examiner of the Fisher application rejected the claims for lack of utility under 35 U.S.C. § 101 and lack of enablement under 35 U.S.C. § 112, first paragraph. The Board affirmed the rejections. In upholding the rejection, the Court cited the guidelines in MPEP § 2107.01(I) that state a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. The Court noted the Applicants' admission that the underlying genes had no known functions, and that "[e]ssentially, the claimed ESTs act as no more than research intermediaries that may help scientists to isolate the particular underlying protein-encoding genes and conduct further experimentation on those genes". Id., at 1373. Accordingly, the Court found the ESTs to be mere "objects of use-testing", upon which scientific research could be performed with no assurance that anything useful will be discovered in the end. Id., *citing* Brenner, 383 U.S. at 535. Fisher's asserted uses represented merely hypothetical possibilities, objectives which the claimed ESTs, or any other EST for that matter, could possibly achieve, but none for which they have been used in the real world. For example, Fisher asserted that the ESTs could be used to identify polymorphisms or to isolate promoters. Nevertheless, in the face of a utility rejection, Fisher did not present any evidence showing that the ESTs had been used in either way. Id. Since nothing was known about the genes or proteins corresponding to the claimed ESTs, nothing set the claimed ESTs apart from the more than 32,000 ESTs disclosed in the application or from

any EST derived from any organism. Id., at 1374. In other words, any EST could be used to isolate any promoter. Furthermore, the use of the ESTs to actually identify the associated gene would constitute significant further experimentation, rendering the ESTs unable to be used in their current form. Ultimately, Fisher's ESTs were deemed only to be research intermediaries in the identification of underlying protein-encoding genes of unknown function. Id., at 1373.

In contrast to the invention of Fisher, the peptide of the instant invention is known to be a fragment of apolipoprotein J precursor protein having the amino acid sequence (i.e. structure) LFSDSPITVTVPVEVSR. Furthermore, the claimed peptide is disclosed as a marker of a specific disease condition, Alzheimer's disease. Any skilled artisan, without significant further research, could utilize the mass spectral profile of the claimed peptide, shown in Figure 2, as a reference for comparison with mass spectral profiles obtained from an unknown sample to screen the sample for a link to Alzheimer's disease through comparison of expression patterns.

Thus, Applicants respectfully submit that the Examiner's attempt to draw a parallel between Fisher and the instant application fails to support her finding a lack of specific and substantial utility, as the facts in Fisher are not akin to the instant application.

It is clear, from consideration of all of the foregoing remarks, that the claimed invention has a specific and substantial utility. Thus, Applicants respectfully submit that the Examiner has failed to make a *prima facie* showing for lack of specific and substantial utility.

2. *The Examiner Improperly Finds Applicants' Asserted Utility
Lacking in Credibility*

The Examiner does not doubt or dispute the results of differential expression of the instant claimed protein 2-18 of SEQ ID NO:1. The main point of disagreement appears to be the interpretation of these results and what constitutes a specific, substantial and credible utility. Thus, the Examiner appears to believe that the showing of differential expression of the claimed peptide in Alzheimer's disease as compared to expression in age-matched controls is not sufficient to indicate that the claimed peptide could be used as a marker for Alzheimer's disease.

Applicants note that it is improper for Office personnel to merely question operability. Factual reasons must be set forth which would lead one of skill in the art to question the objective truth of the statement of operability. MPEP § 2107.02(IV).

The Examiner provides her opinion on what one of skill in the art would know. For example, the Examiner states that one skilled in the art readily appreciates that detection of differentially expressed proteins represents only the first step in identification of molecules that have a diagnostic potential and that one skilled in the art readily appreciates that many factors have a link to or are associated with a particular pathological condition. However, the Examiner does not provide reasoning or references evidencing why one of skill in the art would "readily appreciate" these things.

Furthermore, the Examiner requires Applicant to provide complete characterization of the claimed peptide, including data indicating what amount of the

claimed peptide is diagnostic of Alzheimer's disease, to establish a utility for the claimed peptide.

The instant situation is akin to that in Cortright. Cortright's invention was drawn to a method for treating baldness by applying Bag Balm (a commercially available product used to soften cow udders) to human scalp. The Examiner of the Cortright application rejected the claim drawn to this invention under 35 U.S.C. § 101 as lacking utility. According to the Examiner, Cortright's statement of utility, i.e. her claims of treating baldness, were not credible because baldness was generally accepted in the art as being incurable. The Examiner therefore required clinical evidence to establish the claimed utility, which Cortright did not supply. Cortright, 165 F.3d at 1355.

The Board reversed the rejection under 35 U.S.C. § 101 because the Examiner did not set out sufficient reasons for finding Cortright's statements of utility incredible. The Board additionally noted that there is no per se requirement for clinical evidence to establish the utility of any invention. Id.

Applicants respectfully submit that the Examiner has similarly erred by improperly questioning the operability of the invention, in that she states what one of skill in the art would believe without providing evidence to support her conclusion. Additionally, Applicants respectfully submit that the Examiner has further erred by requiring Applicants to provide "complete characterization" of the claimed peptide in order to establish utility since precedent dictates that evidence of absolute certainty is not required.

Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983), *cert. denied*, 469 US 835 (1984);

MPEP § 2107.02(III)(A). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e. "question") the truth of the statement of utility. MPEP § 2107.02(III)(A). Alternatively, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. MPEP § 2164.07(I)(C).

Furthermore, an Examiner must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill in the art would not believe the applicants' assertion of utility. Brana, 51 F.3d at 1568; MPEP § 2107.01(III).

The prior art recognizes that when a peptide is identified in a body fluid sample from an Alzheimer's patient or appears to be differentially expressed between an Alzheimer's disease patient and a "normal" patient (healthy with regard to Alzheimer's disease), it is immediately recognized as diagnostically valuable, even if the involvement of the peptide in the pathology of Alzheimer's disease is unknown. This practice has been known in the art since at least 1992. See, the abstract of Gunnensen et al. (Proceedings of the National Academy of Science USA 89(24):11949-11953 1992, copy attached hereto as part of the Evidence Appendix) in which the detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer's disease patients lead to the suggestion of glutamine synthetase as a potential diagnostic marker for Alzheimer's disease. Since these practices are common, it is reasonable to believe that when one of skill in the art observes the differential expression of the claimed peptide between Alzheimer's disease patients and non-diseased age-matched control patients; one of skill in the art would, more likely than

not, connect this peptide with potential diagnostics and/or therapeutics for Alzheimer's disease.

Furthermore, Applicants respectfully submit that one of ordinary skill in the art would find the suggestion of a link between the claimed peptide (amino acid residues 2-18 of SEQ ID NO: 1), a fragment of apolipoprotein J precursor protein, and Alzheimer's disease to be reasonable because there is a known association between Alzheimer's disease and apolipoprotein J.

A neuroprotective role has been suggested for apolipoprotein J. See, Giannakopoulos et al. Acta Neuropathology (Berl.) 95(4):387-394 1998, abstract attached hereto as part of the Evidence Appendix. Additionally, it has been suggested that in Alzheimer's disease low cellular expression of apolipoprotein J may be associated with neuronal degeneration and death. Id. Giannakopoulos et al. Thus, considering that their data was in agreement with prior art data, the instant inventors hypothesized that the absence of the claimed peptide in Alzheimer's disease may indicate loss of neuroprotection.

The claimed peptide (amino acid residues 2-18 of SEQ ID NO: 1), elucidated from and differentially expressed in diseased versus normal samples, is identified as a fragment of apolipoprotein J precursor protein at page 46 of the specification as originally filed and is consistently replicated in the sample population. The gel shown in Figure 1 demonstrates that this peptide was identified in age-matched control patients but absent in Alzheimer's patients.

One of ordinary skill in the art would be aware of the involvement of apolipoprotein J in the pathology of Alzheimer's disease. Therefore, one of ordinary skill

in the art would recognize the linkage between the claimed peptide (amino acid residues 2-18 of SEQ ID NO: 1); apolipoprotein J and the degeneration of neurons in Alzheimer's disease and thus would also find the suggestion of this peptide as a marker for Alzheimer's disease to be entirely reasonable.

One of ordinary skill in the art would conclude, based upon all of the foregoing remarks, that the asserted utility for the claimed peptide, use as a marker for Alzheimer's disease, is more likely than not true. Thus, Applicants respectfully submit that the Examiner has failed to make a *prima facie* case for lack of credible utility.

**B. The Examiner Erred in Rejecting Claim 1 under 35 U.S.C. § 112,
First Paragraph.**

1. The Examiner Improperly Finds the Invention Nonenabled

Claim 1, as shown in the attached Claims Appendix, stands finally rejected under 35 USC § 112, first paragraph.

It is well established that the enablement requirement of 35 U.S.C. § 112 incorporates the utility requirement of 35 U.S.C. § 101. Fisher, 421 F.3d at 1378. Where a written description fails to illuminate a credible utility, the PTO will make both a Section 112 rejection for failure to teach how to use the invention and a Section 101 rejection for lack of utility. Cortright, 165 F.3d at 1355. “If [certain] compositions are in fact useless, [a] specification cannot have taught how to use them.” Id.

In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101. As the Court of Customs and Patent Appeals stated in In re Langer:

As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope. Langer, 503 F.2d at 1391 (emphasis in original).

The “Langer” test for utility has been used in evaluation of rejections under 35 U.S.C. § 112, first paragraph, where the rejection is based on a deficiency under 35 U.S.C. § 101. An examiner cannot make this type of rejection, however, unless it has reason to doubt the objective truth of the statements contained in the written description. Cortright, 165 F.3d at 1357. A reason to doubt an asserted utility may be established when the description “suggests an inherently unbelievable undertaking or involves implausible scientific principles.” Brana, 51 F.3d at 1566.

In the present application, the Examiner rejects Claim 1 under 35 U.S.C. § 112, first paragraph, “since the claimed invention is not supported by either a clear asserted utility or well established utility for the reasons set forth [in the Examiner’s rejection under 35 U.S.C. § 101] . . . one skilled in the art clearly would not know how to use the claimed invention.” Applicants respectfully traverse the rejection as Applicants have established in the above remarks that the claimed invention has a specific and substantial credible utility.

A skilled artisan could easily follow the methodology for elucidating the presence of the claimed peptide (amino acid residues 2-18 of SEQ ID NO: 1), as disclosed in the patent application (and reiterated *supra*), on a non-differentiated patient population, in order to discern members of the population who manifest Alzheimer’s disease.

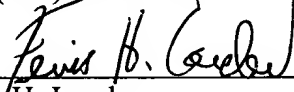
Thus, one of skill in the art clearly would know how to use the claimed peptide (amino acid residues 2-18 of SEQ ID NO: 1) as a marker for Alzheimer's disease. Therefore, Applicants respectfully submit that the Examiner has failed to properly establish lack of enablement.

VIII. CONCLUSION

In conclusion, in light of the foregoing, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for lack of utility and lack of enablement in the present application. Favorable reconsideration of this application and withdrawal of the rejections of claim 1 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph is courteously requested.

Respectfully submitted,

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IX. CLAIMS APPENDIX

Claim 1. An isolated biopolymer marker consisting of amino acid residues 2-18 of SEQ ID NO:1 which evidences a link to Alzheimer's disease.

X. EVIDENCE APPENDIX

A. Appellants rely on four declarations under 37 C.F.R. § 1.132.

1. The Declaration under 37 C.F.R. §1.132, filed on June 9, 2003, was entered into the prosecution record by the Examiner at page 7 of the Office Action mailed on July 18, 2003. It is noted that the figure attached to this declaration contained a typographical error. The top profile is labeled as obtained from the sera of an Alzheimer's patient, however the profile was actually obtained from the sera of a patient age-matched with an Alzheimer's patient. This correction is noted in the Response filed on April 4, 2005 (pages 28-29).

2. The Declaration under 37 C.F.R. §1.132, filed on October 23, 2003, was entered into the prosecution record by the Examiner at page 4 of the Office Action mailed on February 4, 2004.

3. The Declaration under 37 C.F.R. §1.132, filed on October 13, 2005, was entered into the prosecution record by the Examiner at page 2 of the Office Action mailed on November 9, 2005.

4. The Declaration under 37 C.F.R. §1.132, filed on February 9, 2006 was entered into the prosecution record by the Examiner in the Advisory Action mailed on February 27, 2006. It is noted that this declaration is a copy of the declaration filed on October 13, 2005 as the Examiner alleges that the figure originally filed with the declaration (filed on October 13, 2005) was unclear.

B. Appellants rely on two references, both previously presented to the Examiner in the Response filed on April 4, 2005.

1. Gunnersen et al. Proceedings of the National Academy of Science USA 89(24):11949-11953 1992
2. Giannakopoulos et al. Acta Neuropathology (Berl.) 95(4):387-394 1998

Copies of the above-referenced declarations and references are attached hereto as forms the Evidence Appendix.

XI. RELATED PROCEEDINGS APPENDIX

NONE.

There have been no decisions rendered by a court or the Board in the related proceedings identified at Section II, page 5 of this paper.

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICANT

: JACKOWSKI *et al.*

INVENTION:

: **Glycoprotein And Apolipoprotein
Biopolymer Markers Predictive of
Alzheimers Disease**

SERIAL NUMBER

: 09/993,344

FILING DATE

: November 23, 2001

EXAMINER:

: Chernyshev, Olga N.

GROUP ART UNIT

: 1646

ATTORNEY DOCKET NO.

: 2132.096

CERTIFICATE UNDER 37 CFR 1.8(a)

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DECLARATION UNDER 37 CFR § 1.132

I, Ferris H. Lander, do hereby declare as follows:

1. I am a registered Patent Agent and am authorized to represent the inventor's and assignee in the application entitled "Glycoprotein and Apolipoprotein Biopolymer Markers Predictive of Alzheimers Disease", having U.S. Application Serial No. 09/993,344 filed November 23, 2001.

2. In order to provide data which would obviate any rejection/objection regarding completeness of the disclosure, I contacted Dr. George Jackowski, Chairman and Chief Science Officer

of Syn-x Pharma Inc., and asked to be provided with evidence of the absence of the 1873 dalton marker (amino acid residues 2-18 of SEQ ID NO:1) in normal human sera.

3. This declaration (including the attached figure) is provided in order to show a comparison of the indicated disease marker (the 1873 dalton marker; amino acid residues 2-18 of SEQ ID NO:1) to a normal/control group, so as to evidence that the marker is not present in normal human sera.

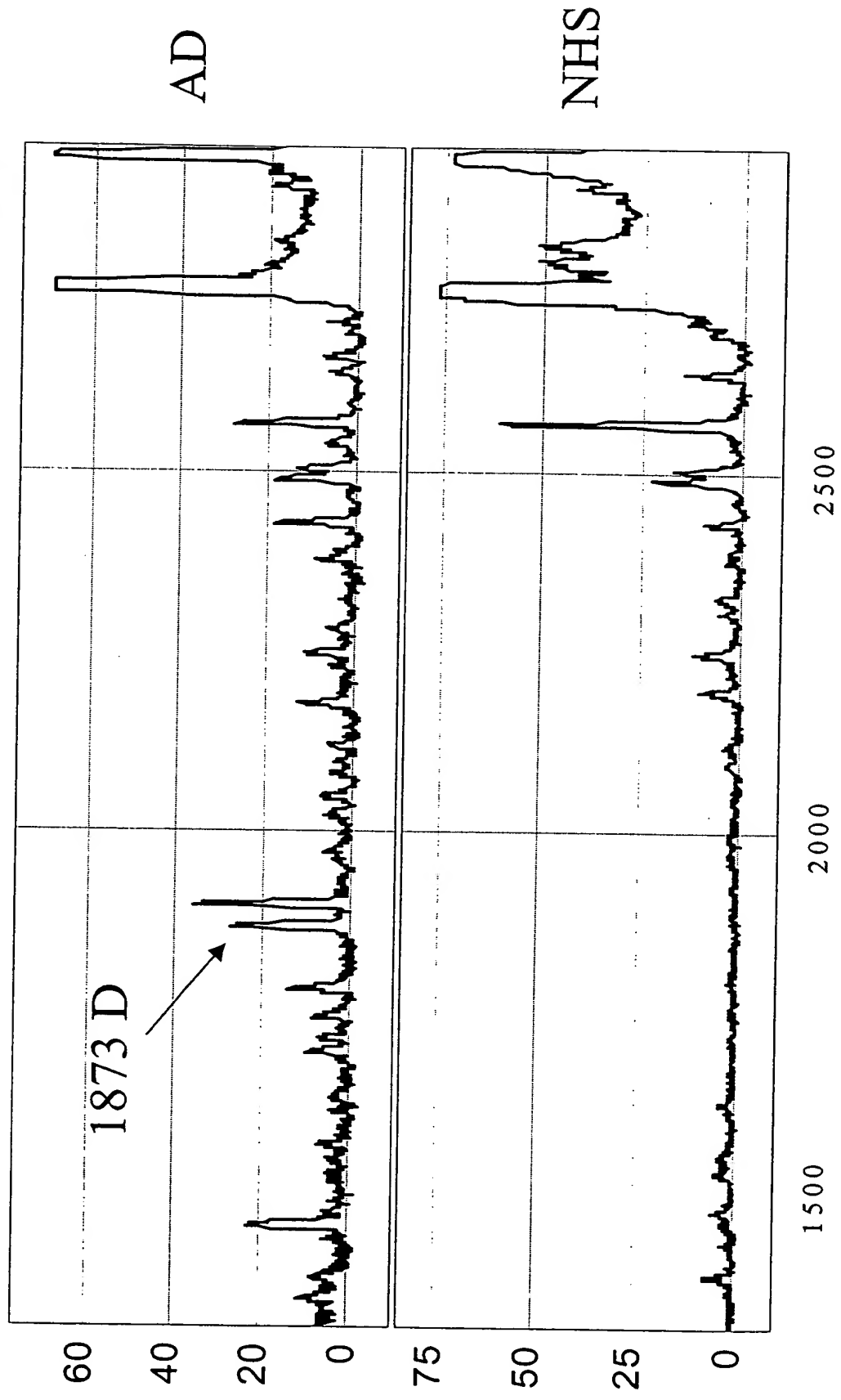
The attached figure, obtained from Dr. Jackowski, provides side-by-side profiles (obtained using techniques of mass spectrometry) of normal human sera versus sera from Alzheimers patients. This profile comparison clearly evidences the absence of the 1873 dalton marker (amino acid residues 2-18 of SEQ ID NO:1) in normal human sera.

The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the Application or any patent issuing thereon.

6/5/2003
Date

Ferris H. Lander
Ferris H. Lander
Reg. No. 43,377


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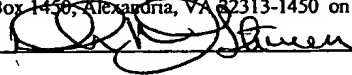
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICANT : Jackowski et al.
INVENTION : Glycoprotein and Apolipoprotein
Biopolymer Markers Indicative of
Alzheimers Disease
SERIAL NUMBER : 09/993,344
FILING DATE : November 23, 2001
EXAMINER : Chernyshev, Olga N.
GROUP ART UNIT : 1646
OUR FILE NO. : 2132.096



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DECLARATION UNDER 37 CFR § 1.132

I, Dr. George Jackowski, do hereby declare as follows:

1. I am Chief Executive Officer and Chief Science Officer of Syn-x Pharma Inc., assignee in the application entitled "Glycoprotein and Apolipoprotein Biopolymer Markers Indicative of Alzheimers Disease", having U.S. Application Serial No. 09/993,344, filed November 23, 2001.

2. In the Office Action mailed on July 18, 2003, claim 1 was rejected under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph because the claimed invention allegedly has no disclosed specific

and substantial utility (101) and thus contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention (112, first paragraph). The Examiner states that the invention is drawn to a biopolymer marker peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 useful in the diagnosis of Alzheimers disease. The Examiner asserts that the experiments disclosed in the specification do not sufficiently support that the claimed peptide is a biopolymer marker of Alzheimers disease. The Examiner is particularly concerned with an alleged lack of controls in the experiments.

3. This declaration is submitted in order to clarify the use of controls in the experiments disclosed in the specification.

4. There are no conventional controls applied in the methods of the instant invention. Both samples from diseased patients and samples from healthy patients (age-matched) are separated by polyacrylamide gel electrophoresis. The gel is then examined in order to identify differences in the bands appearing in diseased and healthy patients (age-matched). The bands, which differ between healthy (age-matched) and diseased patients, are excised and purified from the gel. A determination of upregulation, downregulation, presence and/or absence of the proteins present in the bands is assessed by sample wherein they appear, for example, the claimed peptide fragment was identified and excised from a band which exhibited decreased expression in the diseased samples as

compared with the age-matched samples, thus this can be considered to be down-regulation of the protein in the disease sample as compared to the strong presence of the protein in the age-matched sample. This comparison between two physiological states as evidenced by the bands appearing on the gel represents an inherent control in the experiment. The claimed protein fragments excised from the bands are sequenced and identified through the application of mass spectrometric techniques. It is standard laboratory practice to sequence peptides by mass spectrometry and identify the peptides based upon known sequences available in databases; thus sequencing and comparison of control peptides is not required. One of ordinary skill in the art would be familiar with these standard protocols of mass spectrometry.

The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the Application or any patent issuing thereon.

Oct 20 2003
Date

George Jackowski
George Jackowski

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GROUP ART UNIT

OUR FILE NO.

: Jackowski et al.

: Glycoprotein and Apolipoprotein
Biopolymer Markers Indicative of
Alzheimer's Disease

: 09/993,344

: November 23, 2001

: Chernyshev, Olga N

: 1649

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DECLARATION UNDER 37 CFR § 1.132

I, Ferris H. Lander, do hereby declare as follows:

1. I am a registered Patent Agent and am authorized to represent the inventor's and assignee in the application entitled "Glycoprotein and Apolipoprotein Biopolymer Markers Indicative of Alzheimer's Disease", having U.S. Application Serial No. 09/993,344, filed November 23, 2001.

2. In the Office Action mailed on July 28, 2005, claim 1 (as presented on April 4, 2005) was rejected under 35 USC 101 because the claimed invention allegedly is not supported by either a

specific, substantial, credible or asserted utility or a well-established utility. Claim 1 was also rejected under 35 U.S.C. 112, first paragraph because the claimed invention allegedly contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

3. The attached figure was produced by scanning the original photograph of the gel. No new matter has been added; this figure is simply a clearer copy of Figure 1 as originally filed and is provided for clarification of the presence and/or absence of the bands. The figure entitled "DEAE 3 (Elution) AD vs. Age Matched AD(Control)" represents Figure 1.

The gel shown in the attached figure does not represent new experimentation; the figure shows a clearer image of the original gel made at the time that the experiments described in the instant specification were first carried out.

The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the Application or any patent issuing thereon.

12/11/2005

Date

Ferris H. Lander
Ferris H. Lander
Reg. No. 43,377

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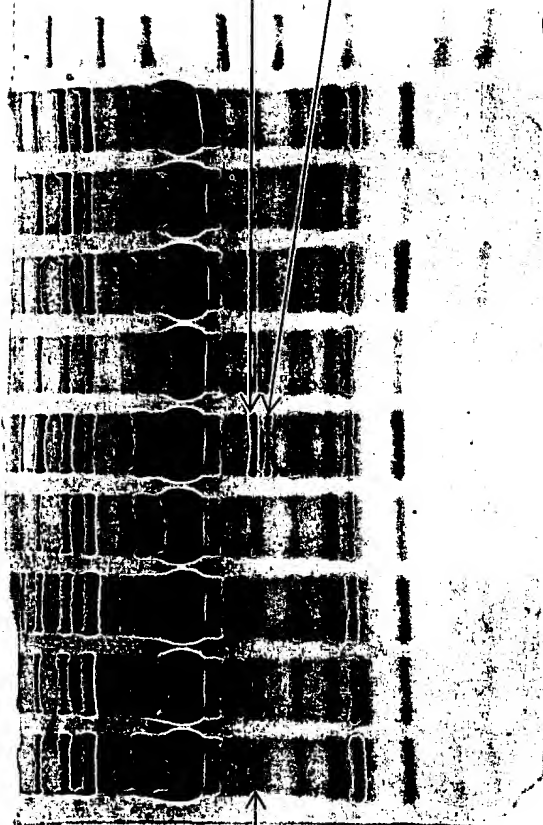
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DEAE 3(Elution) AD vs. Age Matched AD (Control)

AD Age Matched AD

.....



AD-H-S-D3(E) C2

AG-AD-H-S-D3(E) C1

AG-AD-H-S-D3(E) C3

Pooled In-house Normal

AG-AD-H-S-005

AG-AD-H-S-004

AG-AD-H-S-003

AG-AD-H-S-002

AD-H-S-008

AD-H-S-006

AD-H-S-005

AD-H-S-004

High Molecular Weight Standards:

250 Da
150 Da
100 Da
75 Da
50 Da
37 Da
25 Da
15 Da
10 Da

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OUR FILE NO.

: Jackowski et al.

: **Glycoprotein and Apolipoprotein
Biopolymer Markers Indicative of
Alzheimer's Disease**

: 09/993,344

: November 23, 2001

: Chernyshev, Olga N

: 1649

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DECLARATION UNDER 37 CFR § 1.132

I, Ferris H. Lander, do hereby declare as follows:

1. I am a registered Patent Agent and am authorized to represent the inventor's and assignee in the application entitled "**Glycoprotein and Apolipoprotein Biopolymer Markers Indicative of Alzheimer's Disease**", having U.S. Application Serial No. 09/993,344, filed November 23, 2001.

2. In the Office Action mailed on July 28, 2005, claim 1 (as presented on April 4, 2005) was rejected under 35 USC 101 because the claimed invention allegedly is not supported by either a

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specific, substantial, credible or asserted utility or a well-established utility. Claim 1 was also rejected under 35 U.S.C. 112, first paragraph because the claimed invention allegedly contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

3. A similar Declaration (to the instant Declaration) with an attached figure (figure attached hereto is identical to that figure filed with the previous Declaration) was previously filed on October 13, 2005 with the Response to the Office Action mailed on July 28, 2005. However, the Examiner found the Declaration to be insufficient since the copy of Figure 1 filed with the Declaration was allegedly of less clarity than the originally filed Figure 1.

Applicants respectfully disagree with the Examiner's assertion. However, the copy of Figure 1 attached to the instant Declaration will also be forwarded by e-mail to the Examiner such that the figure will not be subjected to the PTO scanning system which may obstruct the clarity of the figure.

4. The claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) was obtained from Band C1 of the gel shown in Figure 1. Band C1 is present in lanes 5-8 (as read from the left) which contain samples obtained from patients age-matched with the patients having Alzheimer's disease. However, Band C1 is absent from lanes 1-4 which contain samples obtained from patients having Alzheimer's disease. Thus, the claimed peptide (amino acid residues 2-18 of SEQ

ID NO:1) is differentially expressed between Alzheimer's disease and a normal (with respect to Alzheimer's disease), age-matched physiological state.

5. In order to further illustrate the point made in item 4, Applicants attach hereto a copy of Figure 1. The figure is entitled "DEAE 3 (Elution) AD vs. Age Matched AD(Control)" and represents Figure 1 as originally filed. This figure was produced by scanning the original photograph of the gel. No new matter has been added; this figure is simply a clearer copy of Figure 1 as originally filed and is provided to clarify the presence, absence and differential expression of the claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1). The gel shown in the attached figure does not represent new experimentation; the figure shows a clearer image of the original gel which was made at the time that the experiments described in the instant specification were first carried out.

The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the Application or any patent issuing thereon.

2/8/2006
Date

Ferris H. Lander
Ferris H. Lander
Reg. No. 43,377

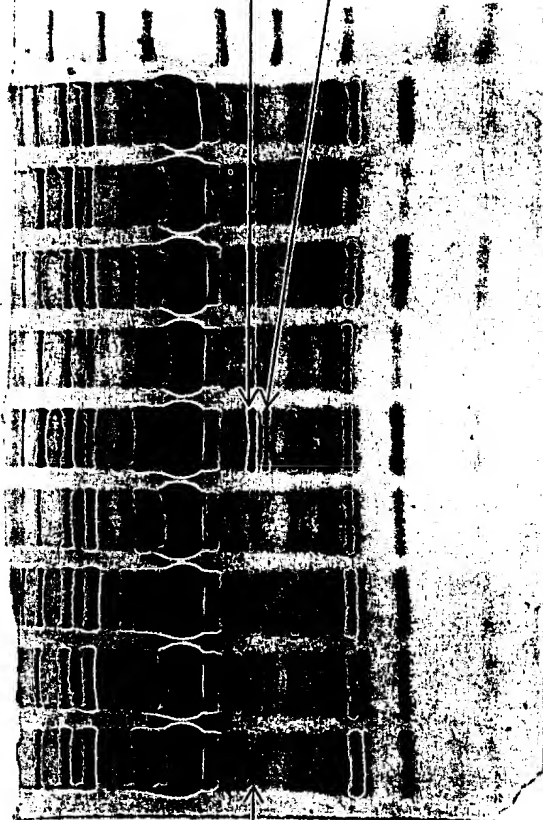
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DEAE 3(Elution) AD vs. Age Matched AD (Control)



AD Age Matched AD

.....



AD-H-S-D3(E) C2

AG-AD-H-S-D3(E) C1

AG-AD-H-S-D3(E) C3

Pooled In-house Normal

AG-AD-H-S-005

AG-AD-H-S-004

AG-AD-H-S-003

AG-AD-H-S-002

AD-H-S-008

AD-H-S-006

AD-H-S-005

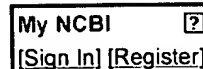
AD-H-S-004

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25 Da
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Detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer diseased patients: a potential diagnostic biochemical marker.

Gunnerson D, Haley B.

Department of Biochemistry, College of Pharmacy, University of Kentucky, Lexington 40536-0084.

In this report, 8- and 2-azidoadenosine 5'-[gamma-32P]triphosphate were used to examine cerebrospinal fluid (CSF) samples for the presence of an ATP binding protein unique to individuals with Alzheimer disease (AD). A 42-kDa ATP binding protein was found in the CSF of AD patients that is not observed in CSF from normal patients or other neurological controls. The photolabeling is saturated with 30 microM 2-azidoadenosine 5'-[gamma-32P]triphosphate. Photoinsertion can be totally prevented by the addition of 25 microM ATP. Photoinsertion of 2-azidoadenosine 5'-triphosphate into the protein is only weakly protected by other nucleotides such as ADP and GTP, indicating that this is a specific ATP binding protein. A total of 83 CSF samples were examined in a blind manner. The 42-kDa protein was detected in 38 of 39 AD CSF samples and in only 1 of 44 control samples. This protein was identified as glutamine synthetase [GS; glutamate-ammonia ligase; L-glutamate:ammonia ligase (ADP-forming), EC 6.3.1.2] based on similar nucleotide binding properties, comigration on two-dimensional gels, reaction with a polyclonal anti-GS antibody, and the presence of significant GS enzyme activity in AD CSF. In brain, GS plays a key role in elimination of free ammonia and also converts the neurotransmitter and excitotoxic amino acid glutamate to glutamine, which is not neurotoxic. The involvement of GS, if any, in the onset of AD is unknown. However, the presence of GS in the CSF of terminal AD patients suggests that this enzyme may be a useful diagnostic marker and that further study is warranted to determine any possible role for glutamate metabolism in the pathology of AD.

PMID: 1361232 [PubMed - indexed for MEDLINE]

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Discovery of the ammonium substrate site on glutamine synthetase, a third cation binding site. *[Protein Sci.* 199.

Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease *Arch Neurol.* 199

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Possible neuroprotective role of clusterin in Alzheimer's disease: a quantitative immunocytochemical study.

Giannakopoulos P, Kovari E, French LE, Viard I, Hof PR, Bouras C.

Department of Psychiatry, University of Geneva School of Medicine, Chene-Bourg, Switzerland. giannako@cmu.unige.ch

Clusterin is a secreted glycoprotein that is expressed in response to tissue injury both in peripheral organs and in the brain. Recent studies have shown a substantial increase in clusterin mRNA in pyramidal neurons of the hippocampus and the entorhinal cortex in Alzheimer's disease (AD), with clusterin immunoreactivity occurring in neuropil threads, neurofibrillary tangles (NFT), and senile plaques. To elucidate further the role of this protein in the degenerative process, a quantitative study of its distribution in the cerebral cortex of non-demented and AD patients, all older than 85 years of age, was performed using immunocytochemistry. Using a stereological approach, we found that in cortical areas affected in AD, such as the entorhinal, inferior temporal and superior frontal cortices, the percentage of NFT-free neurons displaying clusterin immunoreactivity was significantly higher than that in non-demented cases. No such increase in the density of clusterin-immunoreactive neurons was seen in cortical areas that were less affected in the disease process. Furthermore, clusterin immunoreactivity was rarely observed in NFT-containing neurons. In conjunction with previous observations in peripheral tissues, these data suggest that clusterin may have a neuroprotective role, and that in AD, low cellular expression of this protein may be associated with neuronal degeneration and death.

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Active caspase-6 and caspase-6-cleaved tau in neuropil threads, neuritic plaques, and neurofibrillary tangles of Alzheimer's disease. J Pathol. 2004

Apolipoprotein E immunoreactivity within neurofibrillary tangles: relationship to Tau and PHF in Alzheimer's disease. J Neurol. 1995

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